EVIDENCE THAT HISTAMINE IS THE CAUSATIVE TOXIN OF SCOMBROID-FISH POISONING

JASON D. MORROW, M.D., GARY R. MARGOLIES, M.D., JERRY ROWLAND, B.S., AND L. JACKSON ROBERTS, II, M.D.

Abstract *Background.* The highest morbidity worldwide from fish poisoning results from the ingestion of spoiled scombroid fish, such as tuna and mackerel, and its cause is not clear. Histamine could be responsible, because spoiled scombroid fish contain large quantities of histamine. Whether histamine is the causative toxin, however, has remained in question. To address this issue, we investigated whether histamine homeostasis is altered in poisoned people.

Methods. The urinary excretion of histamine and its metabolite, *N*-methylhistamine, was measured in three persons who had scombroid-fish poisoning (scombrotoxism) after the ingestion of marlin. We measured 9α, 11β-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid (PGD-M), the principal metabolite of prostaglandin D_2, a mast-cell secretory product, to assess whether mast cells had been activated to release histamine.

Results. The fish contained high levels of histamine (842 to 2503 μmol per 100 g of tissue). Symptoms of scombrotoxism — flushing and headache — began 10 to 30 minutes after the ingestion of fish. In urine samples collected one to four hours after fish ingestion, the levels of histamine and *N*-methylhistamine were 9 to 20 times and 15 to 20 times the normal mean, respectively. During the subsequent 24 hours, the levels fell to 4 to 15 times and 4 to 11 times the normal values. Levels of both were normal 14 days later. PGD-M excretion was not increased at any time. Two persons treated with diphenhydramine had prompt amelioration of symptoms.

Conclusions. Scombroid-fish poisoning is associated with urinary excretion of histamine in quantities far exceeding those required to produce toxicity. The histamine is most likely derived from the spoiled fish. These results identify histamine as the toxin responsible for scombroid-fish poisoning. (N Engl J Med 1991; 324:716-20.)

SCOMBROID-fish poisoning (scombrotoxism) refers to the clinical syndrome that results from the ingestion of spoiled fish, usually of the families Scombridae and Scomberesocidae. This includes tuna, mackerel, skipjack, and bonito.[1] However, nonscombroid fish, such as mahi-mahi, bluefish, amberjack, herring, sardines, and anchovies, as well as cheese, have also been implicated as causes of scombrotoxism.[2] Scombroid-fish poisoning is the most common cause of ichthyotoxicosis worldwide.[3] In the United States, such poisoning represents one of the major chemical food-borne illnesses reported to the Centers for Disease Control (CDC).[4]

Symptoms of scombroid-fish poisoning usually occur within an hour after the ingestion of spoiled fish and last for several hours.[1] The symptoms include flushing, sweating, nausea, vomiting, diarrhea, headache, palpitations, dizziness, rash, and occasionally, swelling of the face and tongue. Respiratory distress can also occur, and vasodilatory shock has been noted on occasion.[2]

The cause of scombroid-fish poisoning is not clearly understood. The CDC refers to the causative agent as scombrotoxin.[4] The toxin is not present when the fish are caught, but it is produced subsequently during spoilage.[5] Histamine was first suggested as the causative toxin in the 1940s,[6] on the basis of a number of observations. Fish that have caused scombroid poisoning consistently contain large quantities of histamine.[6] Scombroid fish contain substantial amounts of free histidine that can be decarboxylated to form histamine by enteric bacteria present in spoiled fish.[6,7] Furthermore, the symptoms of scombroid-fish poisoning resemble those of histamine toxicity, and improvement in symptoms has been reported after treatment with antihistamines.[8]

The chief factor that has cast doubt on the role of histamine in scombroid-fish poisoning is that although it has been possible to produce mild symptoms of histamine excess after the oral administration of the substance in massive doses to humans, it has not been possible to reproduce the illness with doses comparable to the quantities ingested in fish that have caused scombrotoxism.[9-11] This may be because histamine is absorbed very poorly from the gastrointestinal tract and because the liver and intestinal mucosa have a great capacity to inactivate histamine.[6,11] These results have led to speculation that substances may be present in the spoiled fish that enhance the pharmacologic activity of histamine, facilitate its absorption, or inhibit its inactivation by histamine *N*-methyltransferase, diamine oxidase, or both.[6,12]

The crucial information required to support or refute the speculation that histamine may be the causative toxin of scombroid-fish poisoning — i.e., a direct assessment of whether levels of histamine sufficient to cause toxicity are present in vivo in humans in association with such poisoning — has never been obtained. A recent outbreak of scombroid poisoning at a local cafeteria provided us with the opportunity to address this question.

METHODS

Materials

[$^2H_4$] Histamine and [$^2H_3$] *N*-methylhistamine were obtained from MSD Isotopes (Montreal). The principal urinary metabolite of prostaglandin D_2 — 9α,11β-dihydroxy-15-oxo-2,3,18,19-tetra-

From the Departments of Pharmacology and Medicine (J.D.M., G.R.M., L.J.R.), Vanderbilt University, and the Food Inspection Division, Nashville–Davidson County Metropolitan Board of Health (J.R.), both in Nashville. Address reprint requests to Dr. Roberts at the Department of Pharmacology, Vanderbilt University, Nashville, TN 37232-6602.

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norprost-5-ene-1,20-dioic acid (PGD-M) — was synthesized and converted to the [$^{18}O_4$]-labeled internal standard, as described elsewhere.[13,14]

Measurement of Histamine, *N*-Methylhistamine, and PGD-M in Urine

Histamine, *N*-methylhistamine, and PGD-M were all measured in urine by highly accurate stable-isotope-dilution mass-spectrometric assays.[15-17] The precision and accuracy of the assays were as follows: for histamine, ±3 percent and 98 percent, respectively; for *N*-methylhistamine, ±2 percent and 97 percent; and for PGD-M, ±7 percent and 96 percent. The urinary creatinine concentration was measured by the sodium picrate method with an AutoAnalyzer II (Technicon, Tarrytown, N.Y.). The results of the histamine and *N*-methylhistamine assays were expressed as picomoles per micromole of creatinine, and the results of the PGD-M assay as picomoles per millimole of creatinine. The normal range for each substance was determined by measurements in 20 normal subjects.

Preservation and Handling of the Fish

The marlin implicated in the poisoning incident was caught in Costa Rican waters and flown to Miami. It was shipped to Nashville by refrigerated truck on June 9, 1990. It arrived at the local commercial supplier in Nashville on June 12 and was placed in a walk-in cooler at 1°C. The fish was transported to a local cafeteria on June 14 by refrigerated truck and stored in a walk-in cooler at 7°C. Later that day, the fish was sliced and placed in a reach-in cooler at 9°C. The following morning the fish was cooked and served for lunch. Approximately 50 servings of 100 to 150 g each were prepared, of which 25 were served that day.

In a control study, normal subjects were fed fresh marlin. This fish, obtained on the day of its arrival in Nashville from the same local supplier, was grilled and served immediately after being purchased.

Clinical Study

We studied three persons who had symptoms of scombrotoxism after eating the implicated marlin. Each ate one serving of fish. A fourth person, a chief medical resident at Vanderbilt University, recognized an unusual peppery, metallic taste in the fish. Because he knew that this taste was characteristic of fish implicated in scombroid-fish poisoning,[2,18] he ate only a small portion and did not swallow portions that tasted peppery. He had no symptoms of scombrotoxism subsequently. The poisoned persons were two men and one woman, 35, 27, and 25 years of age, respectively. All were healthy, and none had any history of allergic reactions to fish nor were they taking any medications. Three separate urine samples were collected from each of the four persons for measurements of histamine, *N*-methylhistamine, and PGD-M. The first urine sample was obtained one to four hours after the ingestion of fish. The second was a 24-hour collection begun after the collection of the first sample. The third sample was collected for 24 hours 14 days after the poisoning.

The persons studied were all medical personnel at Vanderbilt University. We were made aware of their cases by another physician at the university who recognized that the symptoms were probably due to scombroid-fish poisoning. Subsequently, the cafeteria was informed of the poisoning, and it stopped serving the fish. It was not possible to identify the other persons who had eaten fish at the cafeteria that day to determine whether any of them had had symptoms of poisoning. Unserved portions of fish were seized and sent to the laboratories of the Food and Drug Administration in Atlanta for an analysis of the histamine content by a standard fluorometric method.[19]

In the control study, we also measured the urinary excretion of histamine and *N*-methylhistamine in three normal subjects after the ingestion of fresh marlin. Each subject ate 125 g of cooked fish. Urine samples were obtained for analysis from each person during the 24-hour period before the fish was eaten. After the ingestion of the fish, the first urine sample voided (obtained within the first 4 hours) and a subsequent 24-hour collection were obtained from each subject. Three portions of the fresh marlin were also analyzed for their histamine content.

Results

Clinical Summary

The three affected persons had symptoms of poisoning that began 10 to 30 minutes after ingestion of the fish and consisted of severe headache, mild nausea, and intense flushing, most notably in the face. One person also had severe diarrhea of sudden onset. One of the three sought care in the Vanderbilt Hospital emergency room and received diphenhydramine (50 mg intramuscularly) that resulted in an amelioration of symptoms within 30 minutes. A second person, a physician, administered diphenhydramine (50 mg intramuscularly) to himself, which also resulted in rapid improvement in symptoms within approximately 30 minutes. The third person did not receive an antihistamine. His symptoms abated after approximately three hours.

In the control study, none of the three subjects who ate fresh marlin had symptoms of scombrotoxism.

Histamine Content of the Ingested Fish

The FDA's analysis of the four random samples of the batch of fish implicated in the poisoning revealed levels of 2495, 1456, 842, and 2503 μmol of histamine per 100 g of fish. Although marlin is a nonscombroid fish and has not previously been reported to cause scombroid poisoning, the histamine content of the fish was very high. The FDA has established a hazard level for poisoning from tuna that contains histamine in concentrations above 450 μmol per 100 g[20]; fresh tuna contains less than 9 μmol per 100 g.[18] The histamine content of the fresh marlin that did not cause symptoms of poisoning was undetectable (<4.5 μmol per 100 g).

Urinary Excretion of Histamine and *N*-Methylhistamine

Initially, we examined whether the ingestion of the fish resulted in the absorption of substantial amounts of histamine or its metabolites by measuring the urinary excretion of the histamine metabolite *N*-methylhistamine (Fig. 1). The urinary levels of *N*-methylhistamine were normal in the urine samples collected from the three persons 14 days after the poisoning. The levels were much higher, however, in the urine samples collected during the symptomatic phase of scombrotoxism in each of these three persons. The initial samples collected one to four hours after the ingestion of the fish contained levels of *N*-methylhistamine 15 to 20 times the normal mean. In the samples collected during the subsequent 24 hours, the levels were still elevated but to a lesser extent, ranging from 4 to 11 times the normal mean.

Thus, the ingestion of the fish resulted in substantially increased urinary excretion of *N*-methylhistamine. These results do not prove, however, that systemic concentrations of free histamine were also

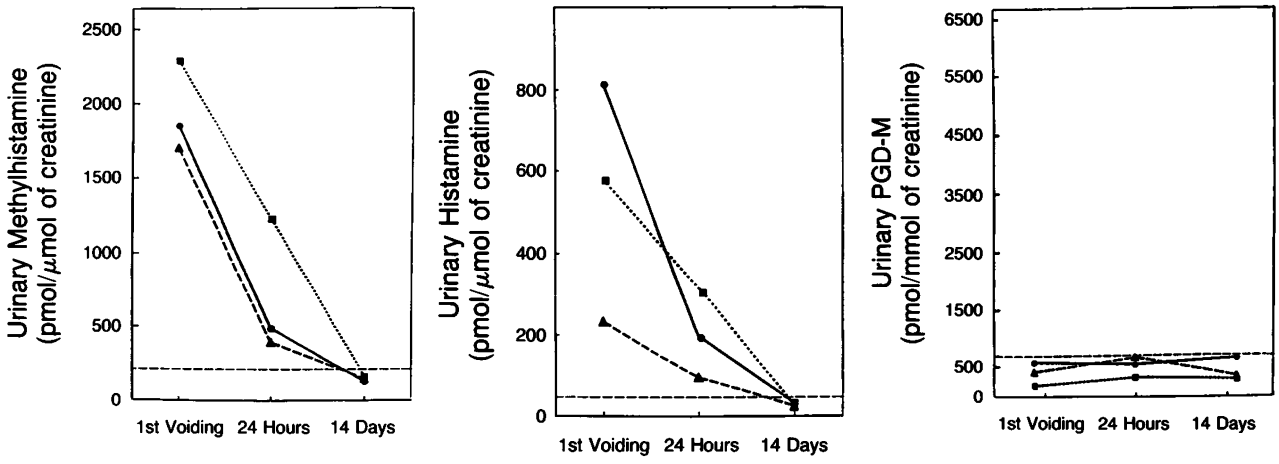

Figure 1. Urinary Excretion of *N*-Methylhistamine, Histamine, and PGD-M in Three Persons with Scombrotoxism.
The first urine voided was collected between 1 and 4 hours after the poisoning, followed immediately by a 24-hour collection and then by a second 24-hour collection 14 days after the poisoning. Each person is indicated by a different symbol. The horizontal lines indicate the normal means +2 SD.

elevated, since ingested histamine could have been metabolized in the intestinal mucosa and liver before entering the systemic circulation.[6] To address this question, we measured the urinary excretion of histamine in the same urine samples. Fourteen days after poisoning, the urinary excretion of histamine in each of the three poisoned persons was normal. However, as we found for the urinary excretion of *N*-methylhistamine, the levels of histamine were elevated in the urine samples collected immediately after the ingestion of the fish. In the urine samples collected between one and four hours after the ingestion of the fish, the levels of histamine were 9 to 20 times the normal mean. In the samples collected during the subsequent 24-hour period, these levels had fallen to 4 to 15 times the normal mean (Fig. 1).

As previously mentioned, one person recognized the peppery, metallic taste of spoiled scombroid fish and thus ate only a small portion of the serving. This person had no symptoms of scombrotoxism, and the urinary levels of both histamine and *N*-methylhistamine were normal both in the urine sample collected soon after the meal and in that collected during the subsequent 24 hours (Table 1). Hence, only those persons in whom scombrotoxism developed had increased circulating concentrations of histamine after ingesting the spoiled fish. In addition, the urinary excretion of both histamine and *N*-methylhistamine remained normal in the three control subjects who ate fresh marlin that contained undetectable quantities of histamine and that did not produce symptoms of poisoning (Table 2).

Table 1. Urinary Excretion of Histamine and *N*-Methylhistamine in the Person Who Ate Only a Small Quantity of the Marlin Implicated in the Poisoning and Did Not Have Scombrotoxism.

Urine Sample	Histamine	Methylhistamine
	pmol/μmol of creatinine	
First voiding after ingestion	32	82
24-Hour collections		
24 hours after first voiding	28	107
14 days later	30	84
Normal mean ±2 SD	25±17	129±78

Assessment of PGD-M Excretion

The increased urinary excretion of histamine in the affected persons could have been due to the ingestion of histamine contained in the fish or the ingestion of other substances present in the fish that evoked the release of endogenous histamine from tissue mast cells. The latter, if it occurs, is unlikely to involve an allergic IgE-dependent mechanism of mast-cell activation, since all persons who eat spoiled scombroid fish have symptoms of poisoning.[5] We and others have found that mast cells activated by either IgE-dependent or independent mechanisms in vitro and in vivo release prostaglandin D_2 along with histamine.[21-26] Therefore, we examined whether there was evidence of increased release of prostaglandin D_2 in the poisoned persons by measuring the urinary excretion of PGD-M. In contrast to the increased urinary excretion of histamine and *N*-methylhistamine, the excretion of PGD-M was normal in all three urine samples from each of the three persons (Fig. 1).

Discussion

Histamine was suggested approximately 50 years ago as the causative agent of scombrotoxism, but its role has remained in question. One reason for the lingering doubt is that it has been impossible to reproduce the illness in normal subjects by administering histamine orally in doses comparable to those ingested when spoiled fish is eaten.[10,11] The crucial information required to resolve this question has not been obtained — namely, whether scombroid-fish poisoning is associated with sufficient increases in circulating hista-

Table 2. Urinary Excretion of Histamine and *N*-Methylhistamine in Three Control Subjects Who Ate Fresh Marlin Containing No Detectable Histamine.*

Urine Sample	Subject 1		Subject 2		Subject 3	
	Histamine	Methylhistamine	Histamine	Methylhistamine	Histamine	Methylhistamine
	pmol/μmol of creatinine					
24-Hour period before ingestion	13	89	24	142	22	150
First voiding after ingestion	17	108	25	124	19	168
Subsequent 24 hours	13	96	16	109	17	167

*See Table 1 for normal urinary concentrations (±2 SD) of histamine and methylhistamine.

mine to cause toxicity. Our results document clearly that this does indeed occur. The urinary levels of histamine in the affected persons far exceeded those associated with symptoms of histamine excess. Kaliner and colleagues found that the urinary excretion of histamine during intravenous infusions of histamine in doses that resulted in flushing, headache, and tachycardia was approximately 34 nmol per hour, or 92 pmol per micromole of creatinine on the basis of an hourly rate of excretion of creatinine of 370 μmol.[27] When first measured, the urinary histamine levels in the three poisoned persons were all higher than 200 pmol per micromole of creatinine (Fig. 1).

Whether potentiators of histamine toxicity were present in the spoiled scombroid fish is unknown.[6,12] It is noteworthy, however, that the increases in the urinary excretion of both histamine and *N*-methylhistamine in the poisoned persons were of similar magnitude. Thus, it is probably valid to conclude that the spoiled fish did not contain substances that potentiated histamine toxicity by inhibiting its inactivation by histamine *N*-methyltransferase.

The failure to find increased endogenous release of prostaglandin D_2 in association with increased levels of histamine suggests that the source of the excess histamine was the fish rather than the release of histamine from mast cells. This is further supported by the finding that the ingestion of fresh marlin containing undetectable quantities of histamine did not result in increased urinary excretion of histamine. Although it is unlikely, we cannot exclude the possibility that other unknown substances may be present in spoiled fish that selectively release histamine but not prostaglandin D_2 from mast cells or that selectively activate basophils, which do not produce prostaglandin D_2, to release histamine.[28-31] Whether histamine is derived from exogenous or endogenous sources, however, does not influence the conclusion that it is the causative toxin of scombroid-fish poisoning.

The identification of histamine as the causative agent of scombrotoxism should serve as the basis for a general public health policy recommendation that persons with scombroid poisoning receive treatment with an antihistamine. Symptoms usually improve with the administration of H_1-receptor–antagonist drugs.[8] The two persons in our study who took diphenhydramine also had rapid amelioration of symptoms. A single report has also described symptomatic improvement after the administration of an H_2-antagonist drug.[32] We and others have demonstrated previously that blood vessels in humans have H_2 receptors and that blocking the vascular effects of histamine requires the blockade of both H_1 and H_2 receptors.[27,33] Thus, there is a rational basis for recommending that persons with scombroid poisoning be treated with antagonists to both H_1 and H_2 receptors in combination.

We conclude that histamine is the toxin responsible for scombroid-fish poisoning. Such poisoning can be prevented effectively by handling and refrigerating fish appropriately.[2] If warming occurs at any point from the time the fish is caught until it is consumed, bacterial proliferation can lead to the production of histamine in quantities sufficient to cause poisoning in the absence of obvious putrefaction.[5] For these reasons, scombroid-fish poisoning will probably continue to be one of the most common causes of ichthyotoxicosis.

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undergo abdominoperineal resection with permanent colostomy. Trials in progress should soon determine how many patients can be adequately treated with extensive surgery (for example, with preservation of the rectal sphincter), concomitant chemotherapy, and radiation.[11] Preoperative or "neoadjuvant" combined-modality treatment specifically tailored to patients at the highest risk for recurrence — an appealing concept — must await more precise staging techniques that will allow the determination of risk before the pathological examination of the surgically removed specimen.

The report of Krook et al. is a step forward, and with the results of the earlier GITSG trial should have a substantial effect on patterns of care for patients who have this common cancer. In view of other recent advances in the treatment of patients with colon cancer[11,12] and the rapid breakthroughs in our understanding of the biology of colorectal cancer, the investment in basic and clinical research over nearly two decades that has resulted from the National Cancer Act seems to be paying off.

New England Deaconess Hospital
Boston, MA 02215 GLENN STEELE, JR., M.D.

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SCOMBROID-FISH POISONING

From Pathogenesis to Prevention

DESPITE dramatic advances in food sanitation during the 20th century, acute food-borne disease caused by infectious agents and chemical toxins remains an important public health problem. From 6 to 81 million cases of such disease are estimated to occur annually in the United States.[1] During the 1980s, several important new causes were identified; examples include verocytotoxin-producing *Escherichia coli* 0157:H7, *Campylobacter jejuni,* and *Listeria monocytogenes.*[1,2] In addition, new vehicles have been implicated in the transmission of previously recognized food-borne pathogens; for example, grade A eggs have been implicated in the ongoing problem of infection with *Salmonella enteritidis.*[2]

Food-borne disease is caused by many bacterial, viral, parasitic, and chemical agents. Many types of foods have been implicated. Foods of animal origin, including meats and dairy products, are involved in the transmission of common bacterial food-borne pathogens, such as salmonella and campylobacter. Shellfish are involved in the transmission of gastroenteritis caused by vibrio infections, hepatitis A, and Norwalk-like viruses. Although they are not often associated with the transmission of bacterial or viral food-borne diseases other than botulism, fish have been implicated in the transmission of two food-borne diseases of public health importance in the United States: scombroid-fish poisoning and ciguatera. These diseases are caused by toxins in the tissue of certain marine fish.[2-4]

National surveillance data on the incidence and relative importance of various etiologic agents of food-borne disease in the United States are based on outbreaks of acute food-borne disease reported by state health departments to the Centers for Disease Control (CDC). In the period 1973 through 1987, from 300 to nearly 700 such outbreaks were reported annually, with the specific etiologic agent identified in only 38 percent of them.[2] For an outbreak to be reported as a cluster of illnesses associated with the ingestion of a food, the incident had to have been first recognized by the consumer or medical personnel, reported to the local health department, and then investigated in sufficient detail to determine that food-borne transmission had occurred. Finally, the incident had to have been reported to the state health department and then to the CDC. The national data undoubtedly underestimate the magnitude of the problem of food-borne disease and are subject to a number of potential biases. For example, outbreaks involving serious disease, disease associated with a short incubation period or a characteristic clinical syndrome, such as scombroid-fish poisoning or ciguatera, or disease affecting large numbers of people are the most likely to be recognized, investigated, and reported. Although the national data have limitations, they are nonetheless useful in providing a perspective on the etiologic agents and foods that cause food-borne disease and in identifying emerging diseases of this type.

From 1973 through 1987, 2841 outbreaks of food-borne disease of known cause were reported to the CDC, involving 124,994 cases. Of these outbreaks and cases, 66 and 87 percent, respectively, were caused by

bacterial agents, 25 and 4 percent by chemical agents, 5 and 9 percent by viruses, and 5 and 1 percent by protozoa and parasites.[2] Among the 697 outbreaks caused by chemical agents, scombroid-fish poisoning and ciguatera were by far the most common, accounting for 29 and 34 percent of the outbreaks and 27 and 24 percent of the cases, respectively. During the past 10 years, much has been learned about the epidemiology and pathogenesis of both these diseases, as well as about paralytic shellfish poisoning and neurotoxic shellfish poisoning, the two types of chemical food-borne disease caused by shellfish in the United States.[3,4]

Each of these diseases caused by toxins in fish or shellfish results from the presence of microorganisms. Scombroid-fish poisoning, most often caused by the consumption of tuna, other scombroid fish, or the nonscombroid fish mahi-mahi,[3-5] has been attributed to the metabolic products of bacterial degradation of fish flesh,[6] whereas ciguatera and paralytic and neurotoxic shellfish poisoning are caused by toxins produced by dinoflagellates that are acquired through the food chain.[4] In contrast to most other food-borne diseases, these illnesses have short incubation periods, typically ranging from a few minutes to a few hours; the symptoms are characteristic and are associated with manifestations outside the gastrointestinal tract — specifically, the skin and the vascular system in scombroid-fish poisoning and the nervous system in the other three diseases.[3-5]

The paper by Morrow et al. in this issue of the *Journal*[7] summarizes the results of a careful investigation of an outbreak of scombroid-fish poisoning involving three persons at a local cafeteria. This investigation illustrates the advances in scientific knowledge that can occur when alert investigators recognize an unusual disease promptly, identify important scientific questions rapidly, and collect appropriate clinical and food specimens for use in addressing these questions. The report also demonstrates the value of a prompt report to appropriate public health authorities in facilitating a rapid response that can prevent additional disease. Recognizing this outbreak required both an alert chief resident, knowledgeable about the characteristics of fish that had caused previous outbreaks of scombroid-fish poisoning (e.g., a peppery, bitter taste), and a cooperative group of patients who, unlike the chief resident, did not suspect a problem with the fish before consuming it.

The clinical features of the outbreak (headache, nausea, and facial flushing in all three persons who became ill and severe diarrhea in one of them) and the incubation period of 10 to 30 minutes are characteristic of scombroid-fish poisoning.[3,4] Besides the suspicion of the chief resident, the rapid occurrence of these characteristic symptoms and the prompt response to the H_1-receptor–antagonist therapy provided to two of the patients undoubtedly hastened the recognition of the cause of this outbreak. Careful laboratory analysis of the promptly collected clinical and fish specimens demonstrated convincingly the role of exogenous histamine in the fish in the pathogenesis of the disease.

Clinicians have long recognized that the symptoms of scombroid-fish poisoning are compatible with a histamine-like reaction, and elevated concentrations of histamine in the flesh of implicated fish have been demonstrated.[3,4,8] The role of histamine in the pathogenesis of the disease has been questioned, however, because previous studies indicated that histamine may not be absorbed from the gastrointestinal tract in amounts sufficient for it to gain access to the systemic circulation and cause the histamine-like manifestations of the illness.[6,9]

The results of the investigation by Morrow et al. clearly show the challenge to those in the food industry and to public health personnel in preventing scombroid-fish poisoning. Inadequate refrigeration of fish permits bacterial growth, which can result in the bacterial decarboxylation of histidine in tissue to histamine.[6,10] The history of the implicated fish in this outbreak demonstrates the increasing complexity of the modern food industry, in which there are opportunities for contaminated foods to be transported rapidly beyond traditional market areas. The authors document the journey of the implicated marlin from the coastal waters of Costa Rica to the cafeteria in Nashville, during which there were numerous opportunities for breakdowns in refrigeration. As with ciguatera, paralytic shellfish poisoning, and neurotoxic shellfish poisoning, cooking does not inactivate the toxin responsible for scombroid-fish poisoning.[3] Fish and shellfish poisonings have been identified more often in coastal areas,[3,4] but the occurrence of this outbreak in an inland area should not be surprising, given the wide commercial distribution of seafood.

Dr. Morrow and his colleagues should be commended for their prompt recognition and reporting of the outbreak to local public health authorities. This rapid notification prevented the exposure of 25 additional people. As is often the case with food-borne outbreaks in food-service establishments, there were no records at the restaurant from which additional patrons could be identified or with which the overall attack rate or the total number of illnesses associated with this fish could be determined. Twenty-one portions of the marlin had been served, however, and additional persons may have been ill.

Several questions remain about the pathogenesis, treatment, and prevention of scombroid-fish poisoning. The factors responsible for the gastrointestinal absorption of large amounts of histamine need to be identified. Since the disease is self-limited, the role of H_1- and H_2-receptor antagonists in therapy remains to be clarified. The overall incidence of food-borne disease, including the incidence of scombroid-fish poisoning, needs to be determined more accurately. The most effective strategies for ensuring adequate refrigeration of fish from the place

where they are caught to the point of consumption need to be identified.

This report shows the value of reporting outbreaks of food-borne disease to public health authorities promptly, as well as the importance of refrigerating perishable foods adequately throughout their transit from point of origin to point of consumption. In addition, this incident provides a reminder for physicians to counsel all patients on the importance of proper food-handling practices and to advise their patients who fish of the need to chill their catch rapidly and maintain adequate refrigeration until the fish is prepared for eating. Finally, the report demonstrates the role of routine surveillance for outbreaks of food-borne disease in providing clinicians with a better understanding of the clinical and epidemiologic clues to the diagnosis of such disease and the value of early diagnosis in facilitating a rapid clinical and public health response.

Centers for Disease Control
Atlanta, GA 30333

JAMES M. HUGHES, M.D.
MORRIS E. POTTER, D.V.M., M.S.

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SMOKING CESSATION AND WEIGHT GAIN

MORE than 1000 years ago, Native Americans were using tobacco, and they were probably aware of its appetite-suppressing and energy-instilling actions.[1] Although scientific papers reporting that the use of tobacco lowered body weight began to appear more than 100 years ago,[2] detailed study of the relation between cigarette smoking and body weight began only 10 years ago.[2-5] There are several reasons for renewed attention to this well-known phenomenon. Cigarette smoking is the single most important preventable cause of death and illness in the United States, resulting in more deaths per year than can be attributed to alcohol, all other addictive drugs, accidents, and suicides combined. In fact, the annual number of deaths from cigarette smoking in the United States (roughly 400,000) is equivalent to the size of the American military force in the Persian Gulf. Despite these powerful statistics, many smokers refuse to try to quit smoking or cannot do it successfully. One reason people give for smoking is to avoid unwanted weight gain. Therefore, studies that help explain the relation between smoking and body weight and, particularly, studies that may reveal how to deal with weight gain that deters smoking cessation are valuable indeed.

The careful epidemiologic study of Williamson et al. in this issue of the *Journal*[6] provides clear evidence that the cessation of cigarette smoking results in weight gain. This conclusion is not new, but for several reasons the study makes a valuable contribution to the literature. Unlike most other studies, this one used prospective longitudinal data, a large sample, and an analytic strategy that controlled for several covariates (among them age, base-line body-mass index, and level of physical activity) that have been ignored in other studies; was longer than others; and addressed the effect of smoking cessation on body weight directly, rather than by studying the effect of smoking on body weight and then extrapolating to the effect of quitting. The results indicate unequivocally that weight gain occurs after smoking cessation.

The paper also provides some new findings. First, the amount of weight gain after the cessation of smoking (2.8 kg in men and 3.8 kg in women) was somewhat greater than the amounts reported in studies in which the period of follow-up was shorter. The likelihood of gaining large amounts of weight (9.8 percent of the men and 13.4 percent of the women gained more than 13 kg) was also greater than previously estimated on the basis of shorter studies. Women who quit smoking gained more weight than men. Most people who gained weight after quitting smoking reached body weights similar to those of age- and sex-matched nonsmokers. Blacks who quit smoking were more likely to gain weight than whites. Finally, those who smoked large numbers of cigarettes gained more weight after quitting. These new findings add to a literature that was summarized and synthesized six months ago in the 1990 report of the Surgeon General, *Health Benefits of Smoking Cessation.*[7]

As with any study, this work has limitations. Most notably, it did not consider the subjects' attempts, if any, to limit weight gain after smoking cessation; compare or analyze the effects of weight gain, body self-image, or perceptions of weight gain on the likelihood of a person's quitting smoking; analyze the results according to the amount of nicotine exposure to establish the role of nicotine; or investigate the mechanisms (e.g., energy intake and expenditure) that cause the changes in body weight in general and the individual differences in weight gain in particular.

Recently, several review papers have been pub-

TABLE 1. SURGICAL STATUS OF BLACK PATIENTS AND WHITE PATIENTS WITH STAGE I OR II NON–SMALL-CELL LUNG CANCER DIAGNOSED BETWEEN 1988 AND 1995 IN SEER AREAS.*

AGE AND STATUS	BLACK PATIENTS	WHITE PATIENTS	P VALUE†
<65 yr			
Underwent surgery (%)	75	84	<0.001
Surgery not recommended (%)	17	8	<0.001
Other or unknown (%)	8	7	0.29
Total no.	929	5,818	
≥65 yr			
Underwent surgery (%)	51	67	<0.001
Surgery not recommended (%)	32	16	<0.001
Surgery contraindicated (%)	5	6	0.50
Patient refused surgery (%)	6	3	<0.001
Other or unknown (%)	6	9	<0.01
Total no.	951	11,039	

*Data are for patients with no previous cancer at any site or with lung cancer as the first of multiple cancers at any site. Patients for whom data were available only from a death certificate or an autopsy report were excluded. SEER denotes Surveillance, Epidemiology, and End Results.

†P values were calculated with the chi-square test.

traindications (due to other medical conditions) were uncommon. The results of an analysis that excluded patients who survived for less than two months (those with a limited opportunity to undergo surgery) were similar (data not shown). Research should focus on why black patients, especially those who are elderly, receive a recommendation for surgery less often than white patients.

ANTHONY P. POLEDNAK, PH.D.
Connecticut Department of Public Health
Hartford, CT 06134

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To the Editor: The article by Bach et al. highlights a pervasive, disturbing, and clearly intolerable feature of our health care system. There are several disparities in health care between blacks and whites in the outcomes of certain diseases. This disparity results in at least 60,000 excess deaths in the black population every year. Compare this figure with the 58,000 deaths that occurred over a 10-year period as a result of the Vietnam War. Our outrage over the needless deaths in Vietnam should be no greater than our outrage at the even larger loss of life in American communities every year. Even after one accounts for some differences in socioeconomic, genetic, social, or cultural factors between blacks and whites, an unexplained factor seems to remain. Overt and subtle racism has been postulated as a possible explanation.[1] The study by Bach et al. appears to confirm that there is a difference in how patients are treated according to their race. Whatever the cause of this difference, the health care system is clearly disempowering and dangerous for black patients.

CHARLES DESHAZER, M.D.
7234 Muncaster Mill Rd., Suite 549
Rockville, MD 20855

1. Charatz-Litt C. A chronicle of racism: the effects of the white medical community on black health. J Natl Med Assoc 1992;84:717-25.

The authors reply:

To the Editor: The correspondents raise some important issues that contribute to our understanding of the disparities in resection rates between black patients and white patients with stage I or II non–small-cell lung cancer. Greenberg et al. previously demonstrated an association between marital status and surgery for lung cancer[1] — this factor was not considered in our first analysis. In our cohort, married patients were more likely than others to undergo surgical resection (P<0.001), but marital status did not confound the primary results (Table 1, next page). Disparities in treatment were present in all marital categories.

We used a validated, claims-based measure of coexisting illness,[2] and explained why the methods we used would be more likely to bias the results in favor of the null hypothesis than to overstate an observed disparity in treatment. The proposal by Campbell and Greenberg to use pulmonary-specific measures of coexisting illness is appealing but cannot be accomplished effectively with codes from the *International Classification of Diseases, 9th Revision*. Similarly, an array of adjustments for socioeconomic status is available, each with its own limitations. We chose a validated method based on U.S. census data that is frequently used in population-based studies.[3,4] There are two problems with using data from the Medicaid Buy-in program as a surrogate variable for poverty. First, the program does not include all persons who are poor, only those who qualify for selected state-specific programs. Second, less than 6 percent of the patients in our sample were enrolled in this program.

Polednak, as well as Campbell and Greenberg, proposes an analysis of the SEER variable for the reason that surgery was not recommended. Because of limited documentation in hospital records, it is not possible to know what factors resulted in the decision not to recommend surgery (Ries L, SEER program: personal communication). However, the analysis Polednak presents is intriguing and suggests that further research on physician–patient interactions will be fruitful. This type of analysis may help explain the treatment disparities that we observed. It should be emphasized that Polednak's analysis, performed with the SEER public-use data base, contains data on patients who were excluded from our analysis because there was no documentation of nodal status, the patient had received a diagnosis of another cancer within two months of receiving the diagnosis of primary lung cancer, or there was no link to Medicare data.[5] The inclusion of these patients in the analysis performed by Polednak does not alter our primary

To the Editor: Casalino argues that measurement of quality may compromise the willingness of caring physicians to go the extra mile. However, the culprit here is not the measurement of quality but rather the financial pressures under which physicians increasingly operate and which compel them to make constant trade-offs between quality and cost. These financial pressures, if anything, make valid quality measurement even more essential. In fact, robust measures of quality include assessments of patients' experiences,[1] allowing people to judge whether a doctor's practice of spending extra time with his or her patients is worth the scheduling delays or perhaps the added cost.

Reports of staggering rates of medical errors,[2] excessive underuse and overuse of proven clinical processes,[3] and insupportable variations in patterns of practice[4] have caused a skeptical public to demand accountability. Well-constructed tools that account both for patients' experiences and for clinical quality will allay some of Casalino's concerns about the unintended consequences of overly narrow measurement. His suggestion that some measures be rotated is a reasonable way of ensuring that physicians do not spend undue effort "playing for the test."[5]

According to Casalino, quality measurement will be a disadvantage to individual physicians because large systems "can afford to purchase expensive data systems and hire quality-improvement experts." This discrepancy is neither unfair nor inappropriate. Although we may wax nostalgic about the shift from "mom and pop" groceries to warehouse superstores, such changes are driven by the perception that larger entities offer better products and more convenience at a lower cost. If the organization of physicians into large medical groups, hospitals, and networks allows us to improve quality and efficiency (a premise that has not been entirely proved), why should this approach not be recognized and rewarded?

In the future, computerized data bases containing easily accessed quality measures will create an educated population that will vote with its feet when selecting providers. Like Casalino, we believe that it is vital that such measures capture both the science and the art of medicine. If solo practitioners are able to match large organizations for quality (and cost), patients may well favor them, especially when the latter seem impersonal and bureaucratic. Likewise, if the large organizations provide care of demonstrably higher quality, patients and payers will most likely migrate to them. Physicians who fail to measure up to the metrics of quality and value will undoubtedly lose patients. This is sad, but it is also inevitable and right.

ROBERT M. WACHTER, M.D.
KAVEH G. SHOJANIA, M.D.
University of California, San Francisco
San Francisco, CA 94143-0120

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Dr. Casalino replies:

To the Editor: Bobrow and Stewart eloquently express the "intuitive conviction" of many physicians that quality measurements lead to unintended consequences. Yet relying only on physicians' professionalism and on "doctors meeting among themselves to discuss . . . cases" has not been enough; I agree with Wachter and Shojania that organized, systematic efforts to improve quality are necessary. Efforts to improve quality require efforts to measure it. As measurements are designed and implemented, explicit attention should be devoted to the anticipation of unintended consequences and to their minimization when they appear undesirable, as I discussed in my article.

Bobrow and Stewart are aware of the problems brought on by quality measurement, problems that they — unlike quality-improvement experts who are not physicians — have experienced firsthand. Yet criticism is not enough: if physicians do not help to create and implement systems to improve quality, others will.

Wachter and Shojania describe the "culprit" as financial pressures that compel "constant trade-offs between quality and cost." This trade-off is disliked by both physicians and patients but is inevitable, since medical resources are not infinite. Despite their assertion that financial pressures are the culprit, they conclude with a very optimistic vision of what economists would call a perfect market: educated consumers, they suggest, will use quality measures (and presumably costs as well) to vote with their feet when selecting physicians, and efficient, high-quality physician organizations will succeed while others will fail. I agree that this would be desirable, insofar as it is possible. But since neither the measures nor the market is likely to be perfect, researchers, purchasers of health care, and policy makers should actively seek to anticipate and to minimize undesirable and unintended consequences of quality measurement and of market competition as well.

LAWRENCE P. CASALINO, M.D., PH.D.
Stanford Coastside Medical Clinic
Half Moon Bay, CA 94019

Diagnosis of Scombroid Poisoning by Measurement of Plasma Histamine

To the Editor: Scombroid poisoning is a form of ichthyosarcotoxism caused by eating spoiled fish, mainly of the scombroid family (such as tuna and bonito).[1] Inappropriate storage of these fish can lead to the decarboxylation of histidine in the flesh to histamine by enterobacteria.[2] The symptoms of histamine poisoning mimic those of an IgE-mediated food allergy: nausea, vomiting, diarrhea, hives, itching, rash, and hypotension can occur within minutes to a few hours of ingesting the fish and last up to 24 hours. We report the occurrence of scombroid poisoning in nine persons.

Ten to 90 minutes after eating a meal together that included cooked tuna, nine persons reported faintness, headache, generalized urticaria, angioedema, and tachycardia. Because the symptoms suggested an allergic reaction, a physician gave them each 4 mg of dexamethasone and one tablet of cetirizine. Five were hospitalized within four hours, with urticaria mainly on the face, trunk, and upper arms;

TABLE 1. PLASMA HISTAMINE CONCENTRATIONS IN SIX PATIENTS WITH TUNA ICHTHYOSARCOTOXISM.

PATIENT NO.	SEX/ AGE (YR)	HISTORY OF ALLERGY	TIME FROM INGESTION OF FISH TO HISTAMINE MEASUREMENT	PLASMA HISTAMINE ON ADMISSION*	PLASMA HISTAMINE AT 24 HR*	OUTCOME AT 24 HR
			hr	nmol/liter		
1	F/19	Asthma, rhinitis	3	21.5	2.5	Flushing, headache
2	M/37	—	3	24.5	4.1	Symptoms resolved
3	M/41	Rhinitis	3	34.9	2.7	Erythema, abdominal pain
4	M/47	—	4	30.6	2.5	Symptoms resolved
5	M/48	—	4	47.8	3.6	Symptoms resolved
6	M/39	—	6.5	6.0	1.8	Symptoms resolved

*The normal value is less than 10.8 nmol per liter.

headache; abdominal pain with diarrhea (in one patient); abdominal pain with vomiting (in one); and upper-limb paresthesia (in two). There was no sign of hemodynamic or respiratory failure. Symptoms resolved within 4 to 6 hours in three patients but persisted for 24 hours in two with a history of allergy.

The results of a quantitative determination of plasma histamine concentrations (Immunotech radioimmunoassay kit) are shown in Table 1. Two pieces of tuna were sent for toxin analysis: a piece of tail did not show histamine, but the other piece had toxic concentrations — more than 100 mg of histamine per 100 g of flesh. The tuna weighed 6 kg, had not been gutted, had been stored in a room at 8°C, and had been eaten four days after being caught.

The association of symptoms of histamine poisoning and the ingestion of fish should alert physicians to the possibility of scombroid poisoning. The tissue histamine concentration is a good indicator of fish spoilage and is a key to the diagnosis. Most of the histamine is produced in the flesh around the intestines and then diffuses into the tissues, so that distant tissue can have misleadingly low concentrations. A finding of increased plasma histamine concentrations soon after the ingestion of contaminated fish (within four hours) confirms the origin of the intoxication, as shown in animals.[3] Elevated urinary excretion of histamine has also been described in three victims of scombroid poisoning,[4] but falsely elevated urinary concentrations are possible (for example, in women with interstitial cystitis). Corticosteroids and H_1 and H_2 antihistamines are effective to treat the symptoms.[5] Since the histamine is exogenous,[4] patients will be able to eat the same (fresher) fish later on.

REGIS BÉDRY, M.D.
Hôpital Pellegrin
33076 Bordeaux CEDEX, France

CLAUDE GABINSKI, M.D.
MARIE-CLAIRE PATY, M.D.
Hôpital Saint-André
33000 Bordeaux, France

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